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A novel synthesis and pharmacological evaluation of a potential dopamine D_1/D_2 agonist: 1-Propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-6,7-diol

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Abstract—Previously, we have demonstrated that enone prodrugs of dopaminergic catecholamines represent a new type of dopamine (DA) agonist. *Trans*-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-6,7-diol (TL-334), the active form of *trans*-1-propyl-2,3,4,4a,5,7,8,9,10,10a-decahydro-1*H*-benzo[*g*]quinolin-6-one (GMC-6650), in vivo showed an extremely potent dopaminergic activity. Here, we report a novel synthesis and a pharmacological evaluation of TL-334 by means of microdialysis.

1. Introduction

Parkinson's disease (PD) is a progressive neurological disorder, which is characterized by the degeneration of nigrostriatal dopaminergic neurons. Currently, the most commonly used medicine for the treatment of PD is *L*-dopa, a bio-precursor of DA. However, the potential neurotoxicity and the long-term complications, such as dyskinesia associated with the use of *L*-dopa, encourage the early use of DA agonists,[1] which mimic the action of DA and possibly counteract the development of dyskinesis.[2]

We have previously described that (*S*)-6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one [(*S*)-PD148903, **1**] is bioactivated in vivo to its corresponding catecholamine [(*S*)-5,6-di-OH-DPAT, **2**] which acts as a potent mixed DA D_1/D_2 full agonist.[3] Similarly, in vivo, **3** was found to display an extremely potent dopaminergic activity with a long duration of action. However, in vitro it does not display any DA receptor binding affinity (D_1–D_5).[4] According to the analysis of brain tissue and blood plasma samples after the rat was given **3**, its catechol form **4**, a well-known D_2 agonist,[5] was found in brain (Fig. 1). Due to the potent dopaminergic activity of **4**, it is interesting to investigate this compound in depth and compare its dopaminergic activity with **3**.

There are a number of test models used for the evaluation of centrally acting DA receptor agonists and antagonists.[6–9] In the models aimed at testing DA agonists, the inhibition seen at low agonist doses is the result of presynaptic DA receptors' stimulation.[10,11] The locomotor facilitation at higher doses is the effect of stimulation of postsynaptic DA receptors.[12,13] Comparing with other catechol-containing DA agonists, compound **4** has been shown to be one of the most effective agents in these models. Microdialysis is a presynaptic model suitable for investigating the biochemical effects of DA agonists in freely moving animals. Stimulation of the autoreceptors leads to a down regulation of DA synthesis and release. However, in freely moving animals, the potential postsynaptic effects of a test compound can be monitored by simply observing the behaviour. Here, we wish to report our results on the microdialysis experiments of **4**.

2. Results and discussion

2.1. Chemistry

The synthetic route of **4** was first developed by Cannon and et al.[5] Since we obtained low yields for some of the

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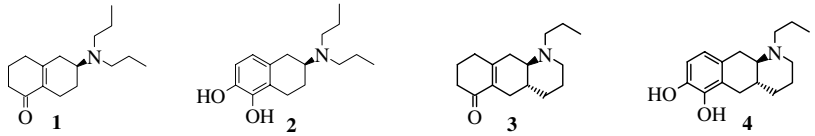
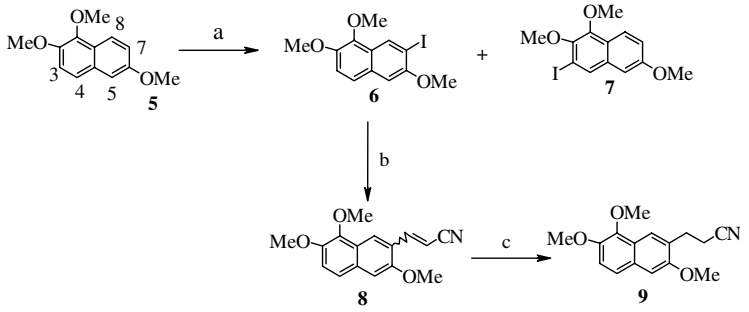


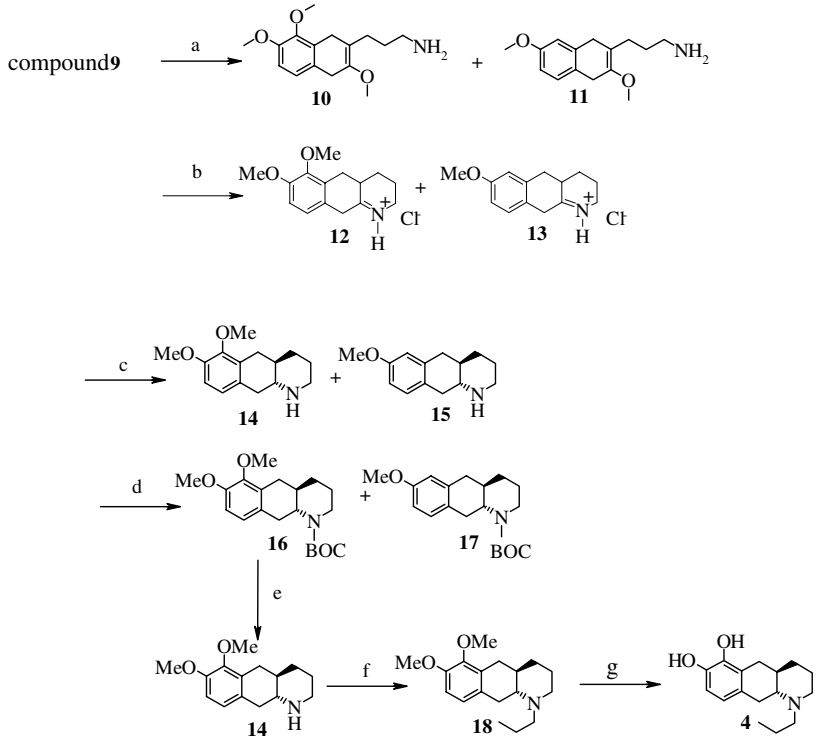
Figure 1. The structures of enones and the corresponding catecholamines (**1** and **2**, **3** and **4**).

intermediates and were not able to reproduce all the steps of that synthesis, we developed a novel synthetic route, based on the work reported by Mellin and Hacksell.[14] The final compound **4** was synthesized according to the strategy displayed in Schemes 1 and 2. Compound **5** was synthesized according to the literature.[15] Lithiation of **5** occurred at both C3 and C7 positions and resulted in a 1:1 mixture of anions. The lithium anions were quenched with iodine to produce in equal amounts the isomers **6** and **7**. These two isomers were separated by column chromatography. The palladium catalyzed Heck reaction[16] of **6** using acrylonitrile and a catalytic amount of $Pd(OAc)_2$ gave a mixture of *E*- and *Z*-isomers of **8** in 70% yield. After hydrogenation with 10% Pd/C, the saturated nitrile **9** was formed which was used for next step without further purification (Scheme 1).

The reduction of **9** with sodium in EtOH mainly occurred in the nitrile-substituted ring, simultaneously, the cyano group was reduced to the primary amine **10**



Scheme 1. Synthesis of **4**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to rt, overnight; −78 °C, I_2, 10 min; (b) $CH_2CH{=}CN$, $Pd(OAC)_2$, Et_3N, CH_3CN, 120 °C, 3 days; (c) 10% Pd/C, 4 bar H_2, rt overnight.



Scheme 2. Synthesis of **4**. Reagents and conditions: (a) Na/EtOH, reflux, 1 h; (b) MeOH, 37% HCl, reflux, 4 h; (c) $NaCNBH_3$; (d) $(BOC)_2CO$, Et_3N, DMAP; (e) TFA, CH_2Cl_2; (f) CH_3CH_2CHO, 1 bar H_2, 10% Pd/C, *n*-propanol, rt, 2 h; (g) HBr 48%, 3 h.

(Scheme 2). It was found that 10% of the dimethoxy-substituted ring was also reduced; subsequently C1 methoxy group was cleaved and the mono-methoxy by-product **11** was formed. Separation of compounds **10** and **11** was found to be very difficult and tedious, therefore, the ring-closure, yielding compounds **12** and **13**, was performed with this mixture. Reduction of these two compounds with $NaCNBH_3$ in MeOH at pH 4 produced exclusively the *trans*-isomers **14** and **15**. These two compounds were separated after protection of the amine with a BOC-group (**16** and **17**). After column chromatography, the BOC-group was cleaved with TFA. The propylation of **14**–**18** was performed via reductive amination with *n*-propionaldehyde under the condition of 1 bar H_2 and 10% Pd/C in *n*-propanol. The methyl group was cleaved with freshly distilled aqueous 48% HBr and gave the target compound **4** (Scheme 2).

2.2. Pharmacology

2.2.1. In vitro function assay. Table 1 shows that the forskolin-stimulated cAMP accumulation in CHO cells transfected with the human D_2 receptor was completely inhibited by **4**, with an EC_{50} of 0.65 nM. Furthermore, a stimulation of cAMP accumulation in CHO cells stably expressing the human recombinant D_1 receptor was found by **4**, with an EC_{50} of 25 nM. The results of these functional assays showed that **4** is a full DA agonist on both D_1 and D_2 receptor subtypes.

2.2.2. Microdialysis study. The biochemical effects of **4** were studied by measuring their effects on the DA levels in the corpus striatum, the brain area of interest in PD, using microdialysis in freely moving rats.[17] The normal DA release before administration of the test compound was set to 100% and the changes in output are expressed in relation to the basal DA levels.

Compound **4** was administered *sc* (1 nmol and 10 nmol kg^{-1}, Fig. 2) and *po* (10 nmol and 100 nmol kg^{-1}, Fig. 3) to male Wistar rats. A maximum of 20% DA decrease was found after *sc* injection of 1 nmol kg^{-1} at 90 min post-administration. At this concentration no stereotyped behaviour (a typical DA D_2 receptor stimulation behaviour) was observed. A significant decrease of DA to 30% of basal levels was observed after administration of 10 nmol kg^{-1} *sc*. The 10 nmol kg^{-1} *sc* injection maintained decreased DA levels in the range of 30–70% for 6 h. During the experiment with 10 nmol kg^{-1} *sc*, **4** induced strong

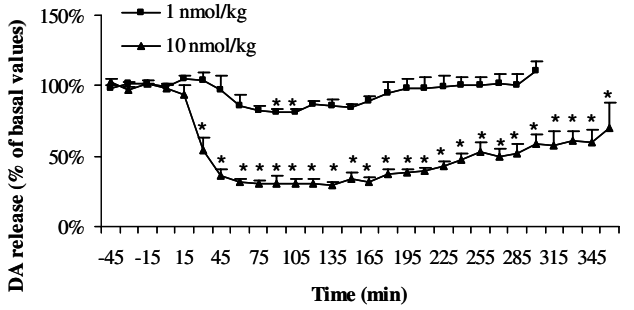


Figure 2. Effect of **4** (1 and 10 nmol kg^{-1} *sc*, ■ and ▲, resp.) on striatal DA release in freely moving rats. The results are the mean (±SEM) of data obtained from four rats (*$p < 0.05$, Student's *t* test).

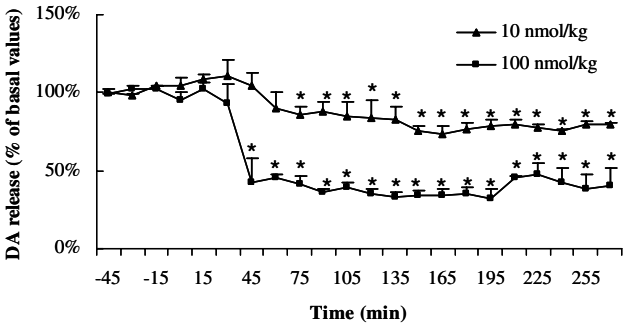


Figure 3. Effect of **4** (10 nmol kg^{-1} and 100 nmol kg^{-1} *po*, ■ and ▲, resp.) on striatal DA release in freely moving rats. The results are the mean (±SEM) of data obtained from four rats (*$p < 0.05$, Student's *t* test).

stereotyped behaviour like locomotor activities, penile grooming, yawning, sniffing, rearing, which is consistent with the postsynaptic effects of a centrally acting DA agonist. This phenomenon demonstrated that at low doses presynaptic DA receptors are stimulated, while high doses stimulate both the pre- and postsynaptic DA receptors.

The oral administration of **4** with the dose of 10 nmol kg^{-1} showed a slight decrease in DA release. Comparing with *sc* administration, this result indicated a low oral bioavailability. However, these results showed that **4** is still 100 times more potent than apomorphine (**19**).[17] Stereotyped behaviour was shown at the dose up to 100 nmol kg^{-1} *po*. At this dose, **4** induced a decrease of the DA levels to 40% of basal values after

Table 1. In vitro receptor functional assay (% intrinsic activity (EC_{50}, nM)) of **4**

	D_1 EC_{50}[d,a] (nM)	IA[c] (%)	D_2 EC_{50}[b] (nM)	IA (%)
Compound **4**	25	95	0.65	100
Dopamine	35	100	43	100
Apomorphine	52	85	4	100
(*S*)-(−)-Pramipexole	>10.000	—	5	100
(*R*)-(+)-SKF38393	30	60	>10.000	—

[a] DA D_1 functional assay on stimulation of cAMP production in CHO cells.
[b] DA D_2 functional assay on inhibition of cAMP formation in CHO cells transfected with the human D_2 receptor.
[c] IA, intrinsic activity.
[d] EC is the concentration (±SD) producing a half-maximal response.

Scheme 3. The auto-oxidation of apomorphine (R = CH_3, **19**) and NPA (R = $CH_2CH_2CH_3$, **20**).

45 min post-administration. The duration of decrease between 60% and 20% was more than 4 h (Fig. 3).

The results of microdialysis experiments also showed that **4** was comparable with apomorphine (**19**), which is a 'stand-by' medicine in the treatment of PD when 'on-off' syndrome occurs after long-term *L*-dopa treatment.[18,19] In the structures of apomorphine (**19**) and NPA (**20**), there is a second aromatic moiety, which makes the C-ring more favorable to aromatization in vivo.[20] Comparing with apomorphine, on this point,**4** is less sensitive to be auto-oxidized (Scheme 3), however, the bioavailability is still low due to the catechol moiety.

3. Conclusion

The results of the functional assay showed that **4** is a full DA agonist on both D_1 and D_2 receptor subtypes. The microdialysis study showed a dose-dependent decrease in the release of DA in the striatum after both *sc* and *po* administration of **4**, and the results indicated that this compound behaves as an extremely potent DA receptor agonist. Although the catechol moiety in **4** is decisive for the low bioavailability, on the other hand, it could also possess the same neuroprotective effects as *R*-(−)-apomorphine (**19**).[21,22] This neuroprotective effect resides in the phenolic moiety, which can act as a radical scavenger.[23] The high efficiency of **4** results in the possibility of administering low dose either by *sc* (10 nmol kg^{-1}) or by *po* (100 nmol kg^{-1}), which could make **4** a candidate for the treatment of Parkinson's disease.

4. Experimental

4.1. General

Melting points were determined in open glass capillaries on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Varian-VXR 300 spectrometer and ^{13}C NMR spectra were recorded at 50.3 MHz on a Varian Gemini 200 spectrometer. The chemical shifts are given in units (ppm) relative to TMS; the splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants are given in Hz. The spectra recorded were consistent with the proposed structures of intermediates and final compounds. Electronic ionization (EI) mass spectra were obtained on Shimadzu QP 5000 GC/MS system equipped with a 17 A GC. Chemical ionization (CI) mass spectra were recorded by the mass spectrometry unit of the University of Groningen. Compounds that were obtained as oil, or as solid in a very small amount, were analysed by high resolution mass spectrometry (HRMS), performed on a JEOL Ms route JMS-660H by the Department of Chemistry, University of Groningen.

All the reagents and solvents were commercially available and were used without further purification with the exception of MeOH, which was distilled from magnesium and dried over 4 Å molecular sieves, and THF which was distilled from sodium/benzophenone and dried on sodium wire.

4.2. Chemistry

4.2.1. 7-Iodo-1,2,6-trimethoxynaphthalene (6). A solution of *n*-BuLi in hexane (1.6 M, 11.3 mL, 18.0 mmol) was added to a solution of **5** (3.27 g, 15.0 mmol) in dry THF (28 mL) under a N_2 atmosphere at −78 °C. After addition, the mixture was allowed to warm to rt and was stirred overnight. The reaction mixture was cooled to −78 °C and a solution of I_2 (4.19 g, 16.5 mmol) in dry THF (6 mL) was added dropwise. After the addition was complete, a saturated aqueous solution of NH_4Cl (11 mL) was added, followed by a saturated aqueous $Na_2S_2O_3$ (6 mL). The volatiles were evaporated. The residue was partitioned between ether and H_2O. The combined organic layers were washed with brine (3× 30 mL), dried over $MgSO_4$. After filtration and evaporation of the solvent, a residue was obtained which was purified by column chromatography (*n*-hexane/ether, gradient), yielding **7** as a white solid (1.8 g, 35% yield). Mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 7.39–7.43 (d, 1H, J = 8.8 Hz), 7.21–7.26 (d, 1H, J = 9.0 Hz), 6.98 (s, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 152.4, 145.5, 140.7, 131.6, 128.9, 124.3, 121.0, 115.1, 103.7, 87.6, 59.7, 55.5, 54.8 ppm; MS (EI) *m*/*z* 344 (M^+). HRMS 343.99149 (obsd). Calcd for $C_{13}H_{13}O_3I$ 343.99095.

4.2.2. 3-Iodo-1,2,6-trimethoxynaphthalene (7). The compound was obtained as the second fraction (1.5 g, 31.6% yield). Mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 8.02–7.98 (m, 2H), 7.12–7.18 (dd, 1H, J = 2.4 Hz, J = 9.3 Hz), 6.94–6.95 (d, 1H, J = 2.4 Hz), 4.02 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 156.2, 145.7, 144.6, 132.5, 130.6, 123.1, 121.9, 117.7, 103.0, 92.0, 59.7, 59.4, 53.8 ppm; MS (EI) *m*/*z* 344 (M^+).

4.2.3. (*E*)-3-(3,7,8-Trimethoxy-2-naphthyl)-2-propenenitrile (8). A mixture of compound **6** (1.8 g, 5.2 mmol), acrylonitrile (0.42 g, 7.9 mmol), $Pd(OAc)_2$ (24 mg, 0.1 mmol), triethylamine (0.53 g, 5.3 mmol) and MeCN (4 mL) was heated in a capped Pyrex flask at 120 °C for 3 days. The cooled reaction mixture was filtered through Celite®, CH_2Cl_2 (100 mL) was added and the solution was washed with 1N HCl (3× 20 mL), brine (3× 20 mL) and dried over $MgSO_4$. After filtration and evaporation of the solvent, a dark residue was obtained which was purified by column chromatography (*n*-hexane:ether = 4:1), yielding **8** as a yellow solid (980 mg, 70% yield). Mp. 97–100 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.62–7.70 (d, 1H, J = 16.9 Hz), 7.36–7.44 (d, 1H, J = 8.8 Hz), 7.20–7.27 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 3.7 Hz), 6.18–6.26 (d, 1H, J = 16.8 Hz), 3.65

(s, 3H), 3.90 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.0, 145.6, 142.2, 129.9, 122.9, 122.4, 122.3, 120.8, 117.5, 116.5, 104.4, 96.7, 59.8, 55.5, 54.0 ppm; MS (EI) *m*/*z* 269 (M^+). HRMS 269.10596 (obsd). Calcd for $C_{16}H_{15}NO_3$ 269.10518.

4.2.4. 3-(3,7,8-Trimethoxy-2-naphthyl)propanenitrile (9). Compound **8** (300 mg, 1.1 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (1:4 mL) and was hydrogenated over 10% Pd/C at 3 bar H_2 for 4 h at rt. The reaction mixture was filtered over Celite®. The filtrate was concentrated to afford **9** as a straw-yellow solid (280 mg, 93% yield). Mp 67–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.44–7.48 (d, 1H, J = 9.0 Hz), 7.21–7.26 (d, 1H, J = 9.0 Hz), 3.91–3.99 (m, 9H), 3.09–3.16 (t, 2H, J = 7.3 Hz), 2.67–2.74 (t, 2H, J = 7.3 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 153.2, 145.5, 141.7, 128.7, 127.0, 122.6, 121.2, 120.9, 118.1, 114.5, 103.6, 59.7, 55.6, 53.8, 26.2, 16.2 ppm; MS (EI) *m*/*z* 271(M^+). HRMS 271.11996 (obsd). Calcd for $C_{16}H_{17}NO_3$ 271.12083.

4.2.5. 3-(3,7,8-Trimethoxy-1,4-dihydro-2-naphthalenyl)-1-propanamine (10). Slices of Na (1.4 g, 0.06 g atom) were added to a refluxing solution of **9** (380 mg, 1.4 mmol) in EtOH (25 mL) under a N_2 atmosphere. After the dissolution of Na was completed (1 h), the heating was interrupted, water (4 mL) and NH_4Cl (3.2 g) were added slowly. The mixture was filtered and the volatiles were evaporated. The residue was partitioned between water and ether. The combined organic layers were washed with water (3× 10 mL) and dried over K_2CO_3. After filtration and evaporation of the solvent, **10** (320 mg) was obtained as a colourless semi-solid. In this mixture, 10% of by-product **11** was observed by GC. This mixture was used in the next step without further purification.

4.2.6. Racemic-*trans*-*tert*-butyl-6,7-dimethoxy-3,4,4a,5,10,10a hexahydrobenzo[*g*]quinoline-1(2*H*)-carboxylate (16). A solution of **10** (280 mg, 1.0 mmol) in MeOH (5 mL) and 37% HCl (1 mL) was heated to reflux under a N_2 atmosphere. After refluxing for 4 h, the solution was concentrated to dryness; an orange oil was obtained (285 mg). The imine **12** (together with by-product **13**) was used in the next step without any purification.

This crude oil (**12** and **13**) was dissolved in MeOH (5 mL) under N_2. The solution was adjusted to pH 4 with the addition of acetic acid. $NaCNBH_3$ (63 mg, 1.0 mmol) was added in portions to the solution. After stirring at rt for 2 h, the mixture was cooled to 0 °C and acidified to pH <2 with conc HCl. The solvent was removed in vacuo and the residue was partitioned between 1 M NaOH and ether. The combined organic layers were washed with brine, dried over K_2CO_3. After filtration and evaporation of the solvent, a crude oil was obtained (220 mg), which was purified by column chromatography (Al_2O_3, CH_2Cl_2/MeOH, gradient), yielding a light yellow oil **14** (contaminated with **15**), 150 mg (60% yield). This yellow oil was dissolved in CH_2Cl_2 (20 mL) under N_2 with cooling. Triethylamine (130 mg, 1.28 mmol) and DMAP (15 mg, 0.12 mmol) were added at 0 °C. Di-*tert*-butyl dicarbonate (160 mg, 0.73 mmol) dissolved in CH_2Cl_2 (5 mL) was added to the mixture dropwise, and the reaction was stirred at rt overnight. The reaction was cooled with ice and 2N HCl was added until pH <3. The acid layer was washed with CH_2Cl_2 (3× 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3× 30 mL), dried over $MgSO_4$. After filtration and evaporation of the solvent, the obtained residue was purified by column chromatography (*n*-hexane/ethyl acetate 9:1) and the two fractions were separated. The first fraction, **17** was obtained as a semi-solid (15 mg, 0.05 mmol), ^{1}H NMR ($CDCl_3$) δ 6.94–6.97 (d, 1H, J = 8.4 Hz), 6.55–6.66 (m, 2H), 3.82–3.89 (dd, 1H, J = 7.5 Hz, J = 13.6 Hz), 3.72 (s, 3H), 3.51–3.60 (td, 1H, J = 4.8 Hz, J = 11.0 Hz), 3.10–3.17 (dd, 1H, J = 4.8 Hz, J = 15.4 Hz), 2.92–3.01 (m, 1H), 2.74–2.80 (dd, 1H, J = 4.4 Hz, J = 16.5 Hz), 2.44–2.64 (m, 2H) 1.49–1.92 (m, 4H), 1.42 (s, 9H), 1.15–1.40 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 156.2, 154.0, 135.3, 128.9, 126.3, 111.8, 110.5, 77.8, 55.8, 53.7, 35.7, 35.1, 33.1, 32.5, 27.1, 23.9, 20.5 ppm; MS (EI) *m*/*z* 317 (M^+); The second fraction as the product **16** (140 mg, 66% yield) ^{1}H NMR ($CDCl_3$) δ 6.67–6.77 (m, 2H), 3.81–3.88 (dd, 1H, J = 7.3 Hz, J = 13.9 Hz) 3.78 (s, 3H), 3.74 (s, 3H), 3.41–3.52 (m, 1H), 2.92–3.16 (m, 3H), 2.56–2.65 (dd, 1H, J = 11.4 Hz, J = 15.0 Hz), 2.20–2.29 (m, 1H), 1.59–1.99 (m, 4H), 1.42 (s, 9H), 1.13–1.40 (m, 1H), ^{13}C NMR ($CDCl_3$) δ 154.0, 148.9, 144.8, 128.6, 127.5, 123.1, 109.0, 77.7, 58.4, 55.4, 54.3, 35.2, 32.74, 32.71, 29.8, 27.1, 24.1, 20.6 ppm; MS (EI) *m*/*z* 347 (M^+). HRMS 347.21046 (obsd). Calcd for $C_{20}H_{29}NO_4$ 347.20963.

4.2.7. Racemic-*trans*-6,7-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (14). To the stirred solution of **16** (120 mg, 0.35 mmol) in CH_2Cl_2(1 mL) at 0 °C, trifluoroacetic acid (1 mL, 5.70 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, and further stirred for 2.5 h. After evaporation in vacuo, the residue was cooled on ice and H_2O (5 mL) was added. The water layer was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3× 30 mL) and the organic layer was dried over K_2CO_3. After filtration and evaporation of the solvent, a light yellow oil **14** (85 mg, 98% yield) was obtained. ^{1}H NMR ($CDCl_3$) δ 6.67–6.76 (dd, 2H, J = 8.4 Hz, J = 17.9 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.06–3.09 (d, 1H, J = 11.7 Hz), 2.93–2.98 (dd, 1H, J = 5.1 Hz, J = 17.2 Hz), 2.65–2.82 (m, 2H), 2.51–2.57 (m, 2H), 2.15–2.19 (dd, 1H, J = 11.7 Hz, J = 17.6 Hz), 1.92–1.95 (d, 1H, J = 12.8 Hz), 1.51–1.69 (m, 3H), 1.37–1.40 (m, 1H), 1.12–1.19 (m, 1H), ^{13}C NMR ($CDCl_3$) δ 148.9, 144.7, 128.9, 127.1, 122.4, 108.8, 58.4, 55.8, 54.3, 45.3, 36.7, 35.3, 30.7, 29.2, 25.4 ppm; MS (EI) *m*/*z* 247 (M^+).

4.2.8. Racemic-*trans*-6,7-dimethoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (18). To a stirred solution of **14** (50 mg, 0.20 mmol) in *n*-propanol (3 mL) under a N_2 atmosphere, *n*-propionaldehyde (60 mg, 1.01 mmol) was added, followed by 10% Pd/C (20 mg). After stirring at rt for 3 h, the mixture was filtered over Celite®. The solvent was evaporated to remove the volatiles. The residue was purified by column chromatography (CH_2Cl_2:MeOH, gradient), a yellow oil **18** was obtained (44 mg, 0.15 mmol, 75% yield). ^{1}H NMR ($CDCl_3$) δ 6.71–6.84 (dd, 2H, J = 8.5 Hz,

J = 10.5 Hz), 3.83 (s, 3H), 3.79 (s, 3H), 2.94–3.12 (m, 2H), 2.23–2.81 (m, 6H), 1.06–2.13 (m, 8H), 0.85–0.92 (t, 3H, J = 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 148.8, 144.4, 128.6, 127.2, 122.6, 108.8, 59.8, 58.4, 54.3, 54.1, 51.4, 35.8, 33.0, 30.8, 29.7, 24.0, 16.0, 10.6 ppm; MS (EI) m/z 289 (M^+).

4.2.9. Racemic-*trans*-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-6,7-diol (4). A solution of **18** (110 mg, 0.38 mmol) in freshly distilled 48% HBr was heated to 135 °C under N_2 for 3 h. The volatiles were evaporated in vacuo to obtain **4** (120 mg, 0.35 mmol, 92% yield) as hydrobromide salt. An analytical amount was recrystallized from MeOH/ether and white crystals were obtained. Mp 309–312 °C; ^{1}H NMR ($CDCl_3$) δ 6.51 (d, 1H, J = 8.0 Hz), 6.39 (d, 1H, J = 8.0 Hz), 2.96–3.50 (m, 5H), 2.65–2.74 (m, 1H), 2.14–2.24 (m, 1H), 1.60–1.92 (m, 5H), 1.20–1.39 (m, 4H), 0.92–0.97 (t, 3H, J = 7.3 Hz); MS (CI) m/z 262 (M^++1).

4.3. Pharmacology

4.3.1. Animals. Animals used in the biochemical and behaviour activity experiments were male rats of the Wistar strain (from Harlan, Netherlands) weighing 300–350 g. The rats were placed in a room with controlled environmental conditions (21 °C, humidity 60–65%; lights on at 8 a.m. and off at 8 p.m. At least for 1 week from arrival until used in the experiments. Animal procedures were conducted in accordance with guidelines published in the NIH guide for the care and use of laboratory animals and all protocols were approved by the Groningen University Institutional Animal Care and Use Committee.

4.3.2. Drugs. All compounds were tested as their hydrochloride salts, except **4** was tested as hydrobromide salt. The drugs were dissolved in physiological (0.9%) saline immediately prior to use. All in vivo experiments were performed at the laboratory animal unit of the Rijksuniversiteit Groningen, the Netherlands, and in vitro experiments were performed at Division of Molecular and Cellular Pharmacology, Lundbeck A/S.

4.3.3. Surgery and brain microdialysis. On-line brain microdialysis in freely moving animals has been described.[24]

4.4. Receptor functional assay

The intrinsic activity of **4** at the DA D_1 and D_2 receptor was determined according to methods previously described[25,26] with some modification.

4.4.1. D_1 cAMP assay. The ability of the compounds to stimulate the D_1 receptor mediated cAMP formation in CHO cells stably expressing the human recombinant D_1 receptor was measured as follows.

Cells were seeded in 96-well plates at a density of 11000 cells/well 3 days prior to the experiment. On the day of the experiment the cells were washed once in preheated G buffer (1 mM $MgCl_2$, 0.9 mM $CaCl_2$, 1 mM IBMX in PBS) and the assay was initiated by addition of 100 μL of the test compound diluted in G buffer.

The cells were incubated for 20 min at 37 °C and the reaction was stopped by the addition of 100 μL S buffer (0.1 M HCl and 0.1 mM $CaCl_2$) and the plates were placed at 4 °C for 1 h. About 68 μL of N buffer (0.15 M NaOH and 60 mM NaAc) was added and the plates were shaken for 10 min. About 60 μL of the reaction mixture was transferred to cAMP FlashPlates (DuPont NEN) containing 40 μL 60 mM NaAc, pH 6.2, and 100 μL IC mix (50 mM NaAc, pH 6.2, 0.1% NaAzid, 12 mM $CaCl_2$, 1% BSA and 0.15 μ Ci/ml ^{125}I-cAMP) were added. Following an 18-h incubation at 4 °C the plates were washed once and counted in a Wallac TriLux counter.

4.4.2. D_2 cAMP assay. The ability of the compounds to whether stimulate the D_2 receptor mediated inhibition of cAMP formation in CHO cells transfected with the human D_2 receptor was measured as follows.

Cells were seeded in 96-well plates at a density of 8000 cells/well 3 days prior to the experiment. On the day of the experiment the cells were washed once in preheated G buffer (1 mM $MgCl_2$, 0.9 mM $CaCl_2$, 1 mM IBMX in PBS) and the assay was initiated by addition of 100 μL of a mixture of 10 μM forskolin and test compound in G buffer.

The cells were incubated for 20 min at 37 °C and the reaction was stopped by the addition of 100 μL of S buffer (0.1 M HCl and 0.1 mM $CaCl_2$) and the plates was placed at 4 °C for 1 h. 68 μL of N buffer (0.15 M NaOH and 60 mM NaAc) were added and the plates were shaken for 10 min. Reaction mixture (60μL) was transferred to cAMP FlashPlates (DuPont NEN) containing 40 μL 60 mM NaAc, pH 6.2, and 100 μL IC mix (50 mM NaAc, pH 6.2, 0.1% NaAzid, 12 mM $CaCl_2$, 1% BSA and 0.15 μCi/mL ^{125}I-cAMP) were added. Following an 18-h incubation at 4 °C the plates were washed once and counted in a Wallac TriLux counter.

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